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Public Health Service

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Memorandum

SUBMISSION: *Statistical Review and Evaluation of BLA #98-0286/0*

FROM: *Vance Berger, Ph.D., HFM-215*

THROUGH: *Peter A. Lachenbruch, Ph.D., Chief, Biostatistics Branch, HFM-215*

TO:
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DATE: *October 21, 1998*

PRODUCT: *Enbrel, or Etanercept, a Human Tumor Necrosis Factor (TNF) Receptor p75-Fc Fusion Protein Produced by Recombinant DNA Technology in a Chinese Hamster Ovary (CHO) Mammalian Cell Expression System*

INDICATION: *Rheumatoid Arthritis (RA)*

APPLICANT: *Immunex*

SUBMISSION DATE: *5/7/98*

MID-CYCLE REVIEW DATE:
8/3/98

ADVISORY COMMITTEE DATE:
9/14/98

1. BACKGROUND:

Etanercept is a competitive inhibitor of the binding of TNF to its cell surface receptors and thereby regulates the biologic activity of TNF. Much of the joint pathology in RA is mediated by proinflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF. Etanercept decreases the levels of soluble adhesion molecules (e.g., E-selectin and intercellular adhesion molecule-1 or ICAM-1) in RA patients. Treatment of RA patients with etanercept also decreased serum levels of IL-6, which is thought to be produced by the cytokine cascade initiated by TNF. ENBREL is contraindicated in patients with or at risk of sepsis syndrome. There was significantly increased mortality with increasing doses of ENBREL in a randomized, double-blind, placebo-controlled Phase II trial evaluating doses of approximately 6 mg/m^2, 18 mg/m^2, and 60 mg/m^2 administered as a single 30-minute IV infusion in patients with sepsis syndrome and hypotension. ENBREL is not approved for marketing in any country. ENBREL was evaluated in the treatment of active RA in three randomized, double-blind, placebo-controlled trials, only one of which was considered to be Phase III. These three trials are described below, but the Phase III study will comprise the focus of this review.

2. LABELING:

The proposed wording of the indications and usage section for the package insert is as follows:

Justification for each of the specific claims of effectiveness included in the indication is presented below, as well as a discussion of the new claims which are included in the draft "Guidance for Industry on Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)" published by the FDA on March 18, 1998.

Claim: Reduction in the Signs and Symptoms of RA

The March 18, 1998 draft guideline suggests that this claim can be established by analyzing the following outcome measures over time in 6-month trials: validated composite endpoints, such as 20% ACR response; and well-accepted sets of signs and symptoms, such as tender and swollen joint counts and physician and patient global assessments. The proposed wording in the package insert, "

" is based on the study of TNFR:Fc in combination with MTX vs. MTX alone.

Claim: Improvement in Physical Function/Disability

At the time of the initiation of the Phase III study, an earlier draft guideline (dated January 3, 1997) was under consideration. This claim was then labeled [redacted]. Accordingly, Protocol 16.0009 was designed to use validated instruments (the HAQ and SF-36) to collect information on functional ability and QOL, as specified by the draft guideline and agreed to by the FDA.

Claim: Major Clinical Response

In the March 18, 1998 draft guideline, major clinical response is defined as continuous 70% ACR response demonstrated in a 6-month trial. Protocols 16.0004, 16.0009, and 16.0014 were designed according to the earlier guideline (January 3, 1997) to analyze 20% and 50% ACR responses. However, measurement of 70% ACR response was retrospectively analyzed in all three studies. Patients in these trials were continued on open-label TNFR:Fc. Therefore, six months of data on achievement of 50% and 70% ACR response as well as continuous 50% and 70% ACR response are available. As the draft guideline has not been finalized and the definition of major clinical response may be revised, data on both 50% and 70% ACR response rates are presented.

3. KEY STUDIES:

3A. PROTOCOL 16.0004, "A Multicenter Phase II Study of Recombinant Human Tumor Necrosis Factor Receptor Fusion Protein (TNFR:Fc) in Active Rheumatoid Arthritis"

3Ai. OBJECTIVES:

The objective was to compare the efficacy and safety of three doses of TNFR:Fc (0.25, 2.00, and 16.00 mg/m^2) with that of placebo when given subcutaneously (SC) twice each week for three months in patients with active RA who failed DMARD treatment.

3Aii. DESIGN:

Study 16.0004 was a Phase II, randomized, double-blind, placebo-controlled multicenter trial with four parallel groups which evaluated 180 patients with active RA who were at least 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs), and had at least 12 tender joints, at least 10 swollen joints, and either ESR>=28 mm/h, CRP>2.0 mg/dL, or morning stiffness for at least 45 minutes. ENBREL doses of 0.25 mg/m^2 (46 patients), 2.00 mg/m^2 (46 patients), and 16.00 mg/m^2 (44 patients) were compared to placebo (44 patients). All treatments were administered subcutaneously (SC) twice per week for three consecutive months. There were 11 centers, all in the United States.

3Aiii. ENDPOINTS:

The primary efficacy parameters were percent changes at Day 85 relative to baseline in painful, swollen, and total joint counts and scores. The secondary efficacy parameters examined were duration of morning stiffness, physician global assessment, patient global assessment, ESR, and CRP. ACR response rates were also calculated, as below:

The American College of Rheumatology (ACR) has defined the ACR20, ACR50, and ACR70 as 20%, 50%, or 70% improvement in tender joint count and swollen joint count, respectively, plus at least 20%, 50%, or 70% improvement in at least three of the five criteria:

1. patient pain assessment;

2. patient global assessment;

3. physician global assessment;

4. patient self-assessed disability;

and

5. acute-phase reactant (ESR or CRP).

3B. PROTOCOL 16.0014, "A Double-Blind, Randomized Study of Recombinant Human Tumor Necrosis Factor Receptor (p75) Fusion Protein (TNFR:Fc) in Patients with Active Rheumatoid Arthritis Receiving Methotrexate (MTX)"

3Bi. OBJECTIVES:

The objective was to compare the safety and efficacy of TNFR:Fc (25 mg SC, twice/week) with that of placebo when given in combination with MTX (15 to 25 mg/week) for six months to patients with active RA.

3Bii. DESIGN:

Protocol 16.0014 was a Phase II/III, randomized, double-blind, placebo-controlled trial which evaluated 89 patients who were at least 18 years old, had received methotrexate for at least six months with a stable dose (12.5 mg/wk to 25 mg/wk) for at least four weeks, and had at least six swollen joints and at least six tender or painful joints. ENBREL 25 mg was compared to placebo, each administered SC twice per week for six months. To qualify for randomization, patients were required to meet the 1987 ARA criteria for RA, to be maintained on a stable weekly dose of 15 to 25 mg MTX for at least 4 weeks, and to be in functional Class I, II, or III by the ACR criteria. Seven centers in the United States participated in the study. The study population consisted of 89 patients randomized in

a 2:1 ratio of TNFR:Fc (n = 59) to placebo (n = 30) and treated concurrently with open-label MTX for 24 weeks (6 months).

3Biii. ENDPOINTS:

The primary efficacy endpoint was a 20% ACR response rate at 6 months. Secondary efficacy endpoints were 20% ACR response at 3 months, 50% ACR response at 3 and 6 months, and percent change from baseline at 3 and 6 months for tender and swollen joint counts, pain as quantified by the patient visual analog scale, patient and physician global assessments, QOL assessment (HAQ), ESR, CRP, rheumatoid factor, and duration of morning stiffness. The 70% ACR response rate was also measured.

3C. PROTOCOL 16.0009, "A Phase III, Double-Blind, Placebo-Controlled, Randomized Study of Recombinant Human Tumor Necrosis Factor Receptor (p75) Fusion Protein (TNFR:Fc) in DMARD-Failing Active Rheumatoid Arthritis"

3Ci. OBJECTIVES:

The objective was to compare the efficacy and safety of two doses of TNFR:Fc (10 and 25 mg) with that of placebo when given SC twice each week for six months in patients with active RA who had failed DMARD treatment.

3Cii. DESIGN:

Study 16.0009 was a Phase III, randomized, double-blind, placebo-controlled multicenter trial with three parallel groups which evaluated 234 patients with active RA who were at least 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs), and had at least 12 tender joints, at least 10 swollen joints, and either ESR>=28 mm/h, CRP>2.0 mg/dL, or morning stiffness for at least 45 minutes. ENBREL doses of

10 mg or 25 mg were compared to placebo. All treatments were administered SC twice per week for six consecutive months.

3Ciii. ENDPOINTS:

The primary efficacy parameter was ACR20 at three months. Secondary efficacy endpoints were ACR20 at six months and ACR50 at three and six months. Other secondary endpoints were tender joint count, swollen joint count, total joint count, duration of morning stiffness, physician and patient global assessment, ESR, and CRP. The ACR70 was also measured.

4. RESULTS:

Three ACR endpoints were measured in each study, some at Months 2, 3, and 6. Consequently, there is a multitude of endpoints, even within each study. The data were found summarized on page 008 of Section 3.1 and in Section 3.8 in Volume 1. In addition, data were submitted electronically.

4A. PROTOCOL 16.0004, "A Multicenter Phase II Study of Recombinant Human Tumor Necrosis Factor Receptor Fusion Protein (TNFR:Fc) in Active Rheumatoid Arthritis"

4Ai. Efficacy

The efficacy data were rearranged from the sponsor's presentation, as in the following tables. The presentation in this review differs from that in the submission in that counts (not proportions) are presented and the counts are based on non-overlapping definitions. For example, there were 10 placebo patients who met the ACR20 criteria at Week 2 in Study 16.0004, and of these ten, one also met the ACR50 criteria. Consequently, nine met the ACR20 criteria and not the ACR50 criteria. This is the rationale for the corresponding entry in the table. This convention

and suggests more comprehensive analyses than simply endpoint-by-endpoint analyses.

Reviewer's Table 4A1: ACR Efficacy Data, Phase II Study 16.0004, Week 2					
p=0.0009	No ACR20	ACR20	ACR50	ACR70	Total
Placebo	34	9	1	0	44
0.25 mg/m^2	31	12	3	0	46
2.00 mg/m^2	24	16	5	1	46
16.00 mg/m^2	22	16	4	2	44
Total	111	53	13	3	180

The one-sided exact (using Monte Carlo sampling from the permutation distribution, with seed — Jonckheere-Terpstra (StatXact) test gives a p-value of 0.0009, with 99% confidence interval (0.0001, 0.0017). This means that larger doses, compared to lower doses, tend to be significantly associated with better ACR response at Week 2.

Reviewer's Table 4A2: ACR Efficacy Data, Phase II Study 16.0004, Month 3					
p=0.0000	No ACR20	ACR20	ACR50	ACR70	Total
Placebo	38	3	2	1	44
0.25 mg/m^2	31	11	4	0	46
2.00 mg/m^2	25	11	6	4	46
16.00 mg/m^2	11	8	16	9	44
Total	105	33	28	14	180

The one-sided exact (using Monte Carlo sampling from the permutation distribution, with seed — Jonckheere-Terpstra (StatXact) test gives a p-value of 0.0000, with 99% confidence interval (0.0000, 0.0005). This means that larger doses, compared to lower doses, tend to be significantly associated with better ACR response at Month 3.

4Aii. Safety

As shown in the sponsor's table on page 215 of Section 3.8 of Volume 1, the 16 mg/m^2 dose was also associated with the highest incidence of a variety of adverse events (AEs). One patient in the placebo group died on study. There were five serious adverse events (SAEs) in the 0.25 mg/m^2 group, two in the 2.00 mg/m^2 group, and two in the 16.00 mg/m^2 group, none of which were considered related to the study medication. Five patients withdrew due to AEs (one in the placebo group, two each in the 0.25 mg/m^2 and 2.00 mg/m^2 groups). Only one of these, occurring in the 2.00 mg/m^2 group, was considered to be related to study medication. There were no Grade 4 AEs, and there were 21 Grade 3 AEs among 19 patients, three of which were considered to be related to study medication.

4B. PROTOCOL 16.0014, "A Double-Blind, Randomized Study of Recombinant Human Tumor Necrosis Factor Receptor (p75) Fusion Protein (TNFR:Fc) in Patients with Active Rheumatoid Arthritis Receiving Methotrexate (MTX)"

4Bi. Efficacy

Reviewer's Table 4B1: ACR Efficacy Data, Phase II/III Study 16.0014, Week 2					
p=0.0003	No ACR20	ACR20	ACR50	ACR70	Total
Placebo	27	3	0	0	30
25 mg/m^2	31	24	2	2	59
Total	58	27	2	2	89

The p-values by the exact permutation Smirnov test (Eplett, 1982; Hilton et. al., 1994; Nikiforov, 1994) are 0.0003 one-sided and 0.0008 two-sided. When using an exact permutation test, normality is not assumed, and the reference distribution is based on the data. For this reason, the reference distribution need not be symmetric, and the two-sided p-value need not be twice the one-sided p-value (but the two-sided p-value cannot be smaller than the one-sided p-value). The low p-values for this

analysis which takes into account the ordering among the four response categories indicates that there is a shift towards better response categories associated with the active treatment group.

Reviewer's Table 4B2: ACR Efficacy Data, Phase II/III Study 16.0014, Month 3					
p=0.0001	No ACR20	ACR20	ACR50	ACR70	Total
Placebo	20	10	0	0	30
25 mg/m^2	20	14	16	9	59
Total	40	24	16	9	89

The p-values by the Smirnov test are 0.0001 one-sided and 0.0003 two-sided. The low p-values for this analysis which takes into account the ordering among the four response categories indicates that there is a shift towards better response categories associated with the active treatment group.

Reviewer's Table 4B3: ACR Efficacy Data, Phase II/III Study 16.0014, Month 6					
p=0.0001	No ACR20	ACR20	ACR50	ACR70	Total
Placebo	22	7	1	0	30
25 mg/m^2	17	19	14	9	59
Total	39	26	15	9	89

The p-values by the Smirnov test are 0.0001 one-sided and 0.0001 two-sided. The low p-values for this analysis which takes into account the ordering among the four response categories indicates that there is a shift towards better response categories associated with the active treatment group.

4Bii. Safety

No patients died during the study. Two patients treated with TNFR:Fc/MTX had three SAEs, but the AEs were considered to be unrelated to study drug. Three patients treated with MTX alone had SAEs. Two patients receiving TNFR:Fc withdrew from the study because of Grade 3 AEs:

but in neither case were the AEs considered by the Investigators to be related to TNFR:Fc. One patient in the placebo/MTX group withdrew from the study due to a Grade 4 SAE (myocardial infarction). No Grade 4 AEs occurred in the TNFR:Fc/MTX group. Seven patients treated with TNFR:Fc reported eight Grade 3 AEs, none of which were considered by the Investigators to be related to study drug. Two patients in the placebo/MTX group had Grade 3 AEs. No Grade 4 laboratory abnormalities occurred in the TNFR:Fc/MTX group.

4C. PROTOCOL 16.0009, "A Phase III, Double-Blind, Placebo-Controlled, Randomized Study of Recombinant Human Tumor Necrosis Factor Receptor (p75) Fusion Protein (TNFR:Fc) in DMARD-Failing Active Rheumatoid Arthritis"

4Ci. Efficacy

The low p-values found by the sponsor's analyses of the individual ACR endpoints were independently confirmed. Despite the fact that the decision was made prospectively to treat ACR20, ACR50, and ACR70 as separate endpoints, more insight is gained by treating them as different cutpoints of the same underlying endpoint. Consequently, they are presented as such. The sponsor's prospectively planned modified intent-to-treat data set (not including patients who were randomized but received no study medication) is presented at each time point. The true intent-to-treat analysis (including all patients randomized) is presented at the prospectively defined primary time point of Month 3, and p-values are provided for this data set.

Reviewer's Table 4C1: Sponsor's ACR Efficacy Data, Phase III Study 16.0009, Week 2 Modified Intent-to-Treat					
	No ACR20	ACR20	ACR50	ACR70	Total
Placebo	79	1	0	0	80
10 mg	63	10	3	0	76
25 mg	54	19	4	1	78
Total	196	30	7	1	234

Reviewer's Table 4C2: Sponsor's ACR Efficacy Data, Phase III Study 16.0009, Month 3 Modified Intent-to-Treat					
	No ACR20	ACR20	ACR50	ACR70	Total
Placebo	62	12	3	3	80
10 mg	42	24	4	6	76
25 mg	30	16	21	11	78
Total	137	52	28	20	234

Reviewer's Table 4C3: Reviewer's ACR Efficacy Data, Phase III Study 16.0009, Month 3 True Intent-to-Treat					
p=0.001	No ACR20	ACR20	ACR50	ACR70	Total
Placebo	65 (78%)	12 (14%)	3 (4%)	3 (4%)	83
10 mg	48 (59%)	24 (29%)	4 (5%)	6 (7%)	82
25 mg	33 (41%)	16 (20%)	20 (25%)	12 (15%)	81
Total	146 (59%)	52 (21%)	27 (11%)	21 (9%)	246

The p-value was p=0.001 for the overall comparison of the three treatment groups (two-sided Cochran-Mantel-Haenszel row-sum test). It was also of interest to compare the 25 mg group to both the placebo group and the 10 mg group (the latter is of interest because it is unaffected by the potential for unmasking of active treatment vs. placebo based on presumed effectiveness of the active treatment

and tell-tale adverse events). The p-value was p=0.0000 (two-sided exact conditional Smirnov test) for comparing 25 mg to placebo, and p=0.0006 (two-sided exact conditional Smirnov test) or p=0.0004 (one-sided exact conditional Smirnov test) for comparing 25 mg to 10 mg.

To study the durability of the ACR20 response, an additional analysis was performed to determine the time until ACR20 was reached only if it lasted through Month 6. That is, each patient is classified as 1 if ACR20 was achieved at Month 1 and lasted through Month 6, 2 if ACR20 was achieved at Month 2 and lasted through Month 6, and so on, or 6 if there was no ACR20 at Month 5 but there was ACR20 at Month 6. Finally, those patients who did not achieve ACR20 at Month 6 were assigned the worst rank of 7 (in this analysis, lower values are better). The results are presented in Reviewer's Table 4C4.

Reviewer's Table 4C4: Time Until ACR20 Lasting Through Month 6, Phase III Study 16.0009
True Intent-to-Treat

p=0.001	1	2	3	4	5	6	7	Total
Placebo	3 4%	1 1%	0 0%	1 1%	1 1%	3 4%	74 89%	83
10 mg	15 18%	7 9%	1 1%	4 5%	8 10%	4 5%	43 52%	82
25 mg	24 30%	6 7%	5 6%	1 1%	5 6%	6 7%	34 42%	81
Total	42	14	6	6	14	13	151	246

The p-value was p=0.001 for the overall comparison of the three treatment groups (two-sided Cochran-Mantel-Haenszel row-sum test). It was also of interest to compare the 25 mg group to both the placebo group and the 10 mg group (the latter is of interest because it is unaffected by the potential for unmasking of active treatment vs. placebo based on presumed effectiveness of the active treatment and tell-tale adverse events). The p-value was p=0.0000 (two-sided exact conditional Smirnov test)

for comparing 25 mg to placebo, and p=0.1318 (two-sided exact conditional Smirnov test) or p=0.0707 (one-sided exact conditional Smirnov test) for comparing 25 mg to 10 mg.

Reviewer's Table 4C4: Sponsor's ACR Efficacy Data, Phase III Study 16.0009, Month 6 Modified Intent-to-Treat					
	No ACR20	ACR20	ACR50	ACR70	Total
Placebo	71	5	3	1	80
10 mg	37	21	11	7	76
25 mg	32	15	20	11	78
Total	140	41	34	19	234

To predict which baseline factors predisposed patients to ACR response (at Month 3), a series of logistic regression models were run. The results were as follows (descriptions of the variable names appear in the second panel):

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate
INTERCP1	1	-0.3239	0.4361	0.5516	0.4577	.
INTERCP2	1	0.9072	0.4421	4.2107	0.0402	.
INTERCP3	1	1.9605	0.4704	17.3716	0.0001	.
BLHAQ	1	0.6071	0.2457	6.1048	0.0135	0.215138
BLJTPNCT	1	-0.0307	0.0121	6.4898	0.0108	-0.267127
BLJTSWCT	1	0.0259	0.0150	2.9891	0.0838	0.173920
PLACEBO	1	1.0144	0.3539	8.2163	0.0042	0.265574
HIGH	1	-0.9267	0.3096	8.9621	0.0028	-0.241104

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Variable Label	Wald Confidence Limits		
		Odds Ratio	Lower Limit	Upper Limit
INTERCP1	Intercept 0			
INTERCP2	Intercept 1			
INTERCP3	Intercept 2			
BLHAQ	Baseline HAQ - Disability Index	1.835	1.134	2.970
BLJTPNCT	Baseline Tender (Painful) Joint Count	0.970	0.947	0.993
BLJTSWCT	Baseline Swollen Joint Count	1.026	0.997	1.057
PLACEBO	PLACEBO=1, OTHER=0	2.758	1.378	5.518
HIGH	25 MG=1, OTHER=0	0.396	0.216	0.726

The fact that weight, height, and body surface area were not retained in the final model suggests that they were not predictive of ACR20 response at Month 3, despite the fact that the dose was constant, and not dependent on the weight of the patient. It was also of interest to study response by center, stratifying by treatment group. These results (only for the two active groups) are as follows:

---------- Treatment=TNFR 10 MG ----------

TABLE OF SITE BY ACRSTAT (patient counts and proportions below them)

SITE(Study Site Number) ACRSTAT

Site	ACR00	ACR20	ACR50	ACR70	Total
17	0	0	1	0	1
	0.00	0.00	100.00	0.00	
36	7	0	0	0	7
	100.00	0.00	0.00	0.00	
39	2	3	0	0	5
	40.00	60.00	0.00	0.00	
102	6	4	1	1	12
	50.00	33.33	8.33	8.33	
105	2	0	0	0	2
	100.00	0.00	0.00	0.00	
107	4	3	1	0	8
	50.00	37.50	12.50	0.00	
200	6	2	1	1	10
	60.00	20.00	10.00	10.00	
260	3	0	0	0	3
	100.00	0.00	0.00	0.00	
272	5	1	0	0	6
	83.33	16.67	0.00	0.00	
274	2	5	0	2	9
	22.22	55.56	0.00	22.22	
343	2	1	0	1	4
	50.00	25.00	0.00	25.00	
351	5	4	0	1	10
	50.00	40.00	0.00	10.00	
407	4	1	0	0	5
	80.00	20.00	0.00	0.00	
Total	48	24	4	6	82

---------- Treatment=TNFR 25 MG ----------

TABLE OF SITE BY ACRSTAT (patient counts and proportions below them)

SITE(Study Site Number) ACRSTAT

Site	ACR00	ACR20	ACR50	ACR70	Total
17	1	1	0	0	2
	50.00	50.00	0.00	0.00	
36	6	1	0	0	7
	85.71	14.29	0.00	0.00	
39	2	2	1	0	5
	40.00	40.00	20.00	0.00	
102	4	2	4	2	12
	33.33	16.67	33.33	16.67	
105	1	0	2	0	3
	33.33	0.00	66.67	0.00	
107	0	2	4	2	8
	0.00	25.00	50.00	25.00	
200	4	1	1	4	10
	40.00	10.00	10.00	40.00	
260	1	1	1	0	3
	33.33	33.33	33.33	0.00	
272	2	1	2	0	5
	40.00	20.00	40.00	0.00	
274	1	2	2	3	8
	12.50	25.00	25.00	37.50	
343	2	0	1	0	3
	66.67	0.00	33.33	0.00	
351	5	2	2	1	10
	50.00	20.00	20.00	10.00	
407	4	1	0	0	5
	80.00	20.00	0.00	0.00	
Total	33	16	20	12	81

4Cii. Safety

No dose-limiting toxicities were observed. No patients died during the study. Five TNFR:Fc-treated patients reported SAEs; none were considered by the Investigators to be related to TNFR:Fc. Seven TNFR:Fc-treated patients withdrew from the trial because of AEs; six (rash, hemoptysis, leukopenia, hypotension, pruritus, and ISRs) were considered by the Investigators or by Immunex to be related to TNFR:Fc. No Grade 4 AEs occurred. Four TNFR:Fc-treated patients

reported Grade 3 AEs; none were considered by the Investigators to be related to TNFR:Fc. No clinically significant laboratory abnormalities were noted in the TNFR:Fc treatment groups.

5. SUMMARY

Enbrel appears to be efficacious, in a dose-related manner. That is, higher doses appear to be more effective than lower doses. It is unclear if doses over 25 mg would be still more effective than any doses studied to date.

6. CONCLUSIONS

The data support the efficacy claim for enbrel. It is unclear, however, if the label should be as broad as is suggested by the sponsor.

REFERENCES

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